## AMENDMENTS TO THE SPECIFICATION

Please replace the first full paragraph of page 4 with the following rewritten paragraph:

Figure 4 depicts [[a]] semi-thin Nissl-stained horizontal sections of the forebrain of Caspase-9 +/- and Caspase-9 -/- mouse embryos at E10.5 (panels A and B). A higher magnification of the boxed areas in panels A and B is shown in panels C and D. Panel E depicts ~~Tunel~~ TUNEL staining of a horizontal brain section of a Caspase-9 -/- mouse embryo at E12. Panel F depicts the distribution of $TUNEL^+$ cells in Caspase 9 +/+ and Caspase 9 -/- embryos. ~~Figure 5 depicts the % survival of Caspase-9 +/+ and Caspase-9 -/- thymocytes in the presence of medium alone ("MED"), 2 μM dexamethasone (DEX), 1 μM staurosporine ("STA") or 1 μg/ml anti-mouse Fas antibody + 30 mg/ml cycloheximide ("FAS") after 6 hours (panel A) or 24 hours (panel B). Genomic DNA isolated from the thymocytes treated as described above are depicted in panels C and D.~~

Please replace the second full paragraph of page 4 with the following rewritten paragraph:

Figure 5 ~~Figure 6~~, panel A, depicts an SDS-polyacrylamide gel electrophoresis of $^{35}S$-methionine labeled caspase-3 treated with an S-100 cytosolic fraction from Caspase-9 +/+ E15.5 and Caspase-9 -/- embryonic brains or thymocytes in the presence or absence of dATP and/or cytochrome c. Panel B depicts an SDS-polyacrylamide gel electrophoresis of $^{35}S$-methionine labeled caspase-3 treated with an S-100 cytosolic fraction from Caspase-9 -/- E15.5 embryonic brains in the presence or absence of dATP, cytochrome c and/or in vitro transcribed and translated Caspase-9.

Please replace the first full paragraph of page 5 with the following rewritten paragraph:

Figure 6 ~~Figure 7~~ depicts brain sections from Caspase-9 +/+ (panel A) or -/- (panel B) E12.5 embryos stained with an antibody specific for activated Caspase-3.

Please replace the last paragraph of page 14 with the following rewritten paragraph:

Although no differences in the kinetics of thymocyte survival were previously observed between wild type and Caspase-3 -/- mice [K. Kuida et al., Nature, 384, pp. 368-72 (1996)], Caspase-9 -/- thymocytes did exhibit variable responses to these apoptosis-inducing stimuli. Caspase-9 deficient thymocytes were resistant to dexamethasone-induced cell death. Caspase-9 -/- staurosporine-induced thymocytes exhibited reduced survival which was comparable to the death seen in controls (~~Figure 5~~ data not shown). In addition, knock-out thymocytes did undergo apoptosis in response to anti-Fas antibody application in a manner similar to wild type cells.

Please replace the first full paragraph of page 16 with the following rewritten paragraph:

While wild type S-100 cytosolic fractions could cleave Caspase-3, cytosolic fractions isolated from Caspase-9 -/- cells could not cleave Caspase-3 (~~Figure 6A~~ Figure 5, panel A). These data demonstrate that Caspase-9 is a necessary caspase upstream in the activation pathway and that the phenotypes we observed in Caspase-9 -/- animals are due to the lack of activation of downstream caspases such as Caspase-3.

Please replace the last full paragraph of page 16 with the following rewritten paragraph:

Moreover, the addition of in vitro translated Caspase-9 to S-100 cytosolic extracts from Caspase-9 -/- brain cells reconstituted the ability to cleave Caspase-3, suggesting that all other required elements are present in Caspase-9 -/- cells (~~Figure 6B~~ Figure 5, panel B).

Please replace the paragraph bridging pages 16 and 17 with the following rewritten paragraph:

Interestingly, and in contrast to a previous report [Liu et al., Cell, 86, pp. 147-57 (1996)], lysates from control cells which could cleave the downstream caspase did not require

additional dATP (~~Figure 6A and 6B~~ Figure 5, panels A and B). This suggests that the intracellular concentration of dATP in the tissues we used was high enough to activate Apaf-1 and that the release of cytochrome c is the required element for initiation of the activation process.

Please replace the second full paragraph of page 17 with the following rewritten paragraph:

In E12.5 wild type and heterozygous embryos, positive staining for activated Caspase-3 was found in the ectodermal surface and sporadically distributed throughout the developing nervous system (~~Figure 7A~~ Figure 6, panel A). Under high magnification, staining for active Caspase-3 was present both in the cytoplasm and in the condensed nucleus (data not shown). In contrast, although CM1-positive cells were seen in the meningeal and ectodermal surfaces of Caspase-9 -/- embryos, no such staining was found within the nervous tissue (~~Figure 7B~~ Figure 6, panel B). Therefore, these results indicate that Caspase-9 is upstream and critical to the activation of Caspase-3 in the developing nervous system in vivo.